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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,748	06/15/2001	Steven M. Ruben	PF523P1	5654

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,748	RUBEN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-14-04; 1-18-05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *97-100,119-127 and 130-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *97-100,119-127 and 130-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

RESPONSE TO AMENDMENT

The amendment to the claims, substitute specification, responses and declaration filed 12-14-04 and 1-18-05 have been entered into the record. Claims 97-100, 119-127, 130-152 are pending and under examiniation.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Objections or Rejections Withdrawn

The objection to the disclosure is withdrawn in view of Applicants' amendments thereto.

The rejection of claims 81, 82, 102-118 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn based on cancellation of the claims.

The rejection of claims 97-101 and 119-143 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn based on the amendment to the claims.

The rejection of claim 99 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' arguments.

The rejection of claims 144 and 145 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the appropriate assurances provided by Applicants representative in the response of 12-14-04.

The rejection of claims 81, 82, 97-143 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the cancellation of the claims or Applicants' amendments.

The rejection of claims 81, 82, 102, 107, 111-118 are rejected under 35 U.S.C. 102(b) as being clearly anticipated byTribouley et al, Biol Chem. 380:1443-1447, December 1999, of record in PTOL-1449) is withdrawn in view of the Applicants' cancellation of the claims.

The rejection of claims 81, 82, 102, 107, 111-118 under 35 U.S.C. 102(b) as being clearly anticipated by Mukhopadhyay et al (The Journal of Biological Chemistry, 274(23):15978-15981, June 4, 1999; of record in PTOL-1449) is withdrawn in view of the Applicants' cancellation of the claims.

Rejections Maintained

Double Patenting

Claims 97-100, 119-152 of this application conflict with claims 3, 4, 5, 6, 7, 17-19, 20, 21, 33 and 35 of Application No. 10/293,418. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of

such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

This is maintained for reasons made of record in the Office Action mailed . Applicants have not addressed this issue and provided no good and sufficient reasons for maintining conflicting claims in duplicate applications. Failure to address this issue in the next reply will be held non-responsive.

Claim 144 and 145 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 33 and 35 of copending Application No. 10/293,418. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented is maintained for reasons made of record in the Office Action Mailed 9-14-04.

Neither Applicants' response or amendment to the claims has not obviated this issue.

Claims 97-100, 119-143 and new claims 146-152 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33 and 35 of copending Application No. 10/293,418 is maintained for reasons made of record in the Office Action Mailed 9-14-04.

Applicants' request that the rejection be held in abeyance until the instant or co-pending Application is in condition for allowance. Applicants' request is noted. However, until the rejection is obviated, it is maintained.

Claims 144 and 145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention is maintained for reasons made of record in the Office Action Mailed 9-14-04.

As to claims 144 and 145, the word ATCC™ is also an active trademark. As such, it should be recognized as such. It should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants have not amended the claims to recite the generic terminology.

New Objections or Rejections Based on Amendment

Specification

The amendment filed 12-14-04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Applicants have amended Table 1, column 3 to change the delineation of the V_L domains in some of the individual human scFv. The response was accompanied by a declaration to attempt to establish that the error was "obvious" is not persuasive for reasons set forth below. Applicant is required to cancel the new matter in the reply to this Office Action.

MPEP 2163.07 (II) indicates that "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)." The declaration of Rodger Smith was filed persuant to 37 C.F.R 1.132 to establish that the errors in the delineation of the VL region in the scFv's of Table 1 were obvious errors and would have been able to be identified and corrected by an antibody scientist. First, Declarant does not establishe that one skilled in the are would have recognized the existance of the errors in the specification. The errors identified were identified post-filing and are not immediately apparent for the

following reasons. Declarant indicates that the antibody scientist would know and be able to correct the identified errors because the specification teaches at paragraph [0069] that it would be routine to align the sequences of the scFvs disclosed in Table 1, against known human germline genes to determine if the closest germline V_L domains is a Vκ or a Vλ. This is not persuasive. [0669] teaches that the individual segments were aligned to the known human germline sequences in "V-BASE" which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website). This passage is seen to teach identification of the closest germline, but does not identify any specific germline, nor does it identify the particular human germline from which the scFv was derived nor does is point to assignment of V_L domains as a Vκ or a Vλ. There is no guidance to do so in the specification. There is no identification of any specific human germline gene nor corresponding protein sequence pointed to by the specification. As such, there is no "obvious" error that one skilled in this art can point in veiw of the general rules of Kabot and Wu et al as (Exhibits F and G) argued by Applicants and Declarant. Further, even if one were to align sequences, Declarant uses a completely different database to make alignments and comparision for the subsequent rationale. There is no showing that the two different databases at the time of invention were identical. There is no direction nor guidance to the IgBLAST database. If the databases were not "identical" then the conclusions based on the closest germline identified cannot not be supported by the evidence presented in the IgBLAST database maintained by the National Centre for Biotechnology. There is nothing in the specification to direct the antibody scientist to the Declarants database and as such conclusions based on use of this database are fundamentally flawed. Further, the conclusions based on the database are flawed because it is readily acknowledged in the exhibit that the database does not include all human germline sequences "no attempt was made ot include all polymorphic forms of germline genes" and not all human germline sequences are known. Applicants assert that "the sequences of most if not all Vκ or a Vλ germline genes were known. This statement is

unsupported by any extrinsic evidence. This is an opinion and while some may be known, it is clear that databases do not include them all, as evidenced by IgBLAST acknowledgement. It is well established in this are that polymorphisms are allelic variation of a germline sequence and therefore are themselves germline sequences. Because such polymorphisms exist and that the database specifically excludes these polymorphisms... there can be no conclusion that the closest match of any scFv is derived from any particular germline unless the match is 100% because all germline sequences are acknowleged not present in the IgBLAST database (see exhibit). Therefore, one skilled in the art cannot conclude that the "closest match" is the germline from which the scFv was derived and thus can be used to correct an obvious error in the delineation of a variable light chain domain, when the germline from which it was derived is unknown, undisclosed and the closest match is at best speculative, regardless of the database used to align the sequences. The situation in regard to the specific database set forth in the specification these issues are unknown, however one skilled in the art would not be able to use that database either for the same reasons presented below for the IgBLAST alignments. Applicants argue once that you align the sequences, one skilled in the art can make corrections in sequences (deletions or insertions) based on alignment to the closest germline match. This reasoning is fundamentally flawed because one can only recognize errors if one is aware and knows the germline sequence from which the V_L domain was derived. This is not taught in the specification nor in the art. One skilled in the antibody art are cannot conclude that the extra amino acids are in Declarant's words ".. most likely arose as a "side-effect" of the cloning strategy used to create the scFvs constructs in the initial generation of the scFv library" because the information provided in the Exhibit of Table I in the Fifth Edition of Kabat et al, page xvi of Exhibit G indicates that the terminal light chain framework 1 domain in the light chain variable domains is 1-23 with an occasional residue at "0". That clearly indicates that this the framework 1 -germline region is not necessarily limited to the 1-23 or 1-22 rules specifically applied by Declarant.

Because the specification does not disclose the particular germline sequence from which the scFv's were derived, one cannot conclude that the "residue" represented as "A", or "L" or "F" residues are not germline variable domain amino acids of a polymorphic germline sequence. There is no explaination of the cloning strategy of the scFv library and how that strategy resulted in the insertion of the alleged "A", "AF" or "AL" residues prior to the V_L domain as asserted and would be so recognized by one skilled in the art. There is no evidence that the cloning strategy employed has this effect. Further, there is no discussion in the specification as filed of the cloning strategy for the scFvs how they were produced such that the skilled artisan would readily conclude that these residues were derived from the specific cloning proceedure. The only description is at [0668] and merely states that an scFv library was screened. Declarant's conclusion is thus mere speculation of a potentical explaination and is not supported by any evidence of the specific cloning strategy employed to make the scFv library, as disclosed in the specification as filed. The other potential explaination is that the germline contained an additional amino acid. The skilled artisan cannot rule this out. Further, one skilled in the art would expect if it was a cloning strategy error then all the errors would be the same and they are not. Therefore, the assertion that the additional amino acids are a result of the method of cloning is unpersuasive. The standard is that would the skilled artisan would recognize the error and the correction. Here, the skilled artisan would not recognize the specific errors because Kabat et al (Exhibit G) teach that the variable domain may have an occasional residue at "0" and therefore cannot immediately and obviously conclude that the delineation of the metes and bounds of the light chain variable domain as set forth in Table 1 was wrong and Applicants new delineation is the appropriate correction, based on the the closest alignment of an admittedly incomplete databse and in view of the absence of specific disclosure of the germline sequences from which the scFv was derived. As such, this is not an obvious error, the error is not obvious, nor is the correction. Therefore, one skilled in the art would not recoginze the error nor Applicants' /

Declarant's solution as the appropriate correction in view of the teaching and guidance of Kabat et al made of record by Declarant. The same rationale applies to the "cloning stratagey" argument made for the missing serine. How does the skilled artisan immediately know that it is serine as opposed to any other residue, or serine plus another residue that is missing ? The error of being too short maybe identified as an error but the solution is not. Declarant's position is a post-facto analysis and is speculative based on flawed reasoning and a specification that does not point one to the specific germline sequences used to recitfy the alleged obvious errors. One must use the actual germline sequence from which the sequence is derived to determine the metes and bounds of the V_L domain and not something that is the closest match in an incomplete database. The skilled artisan may speculate that serine is a candidate, but could not rule out that the actual germline is something different or is serine plus an amino acid at position "0". Declarant points out in Footnote 4 at page 8 of the declaration that SEQ ID NO:1389 and indicates that the first amino acid of the V_L is calculated to be the last serine residue of the linker sequence. Declarant indicates that SEQ ID NO:1389 is most closely related to germline V1-13 which begins with a Q amino acid residue and concludes that it is likely that the sequence of this V_L region was mutated either prior to being cloned into a scFv construct or during passaging or selection of the scFv library. This is not persuasive, based on Applicants own reasoning, the missing residue should be "Q" and not "S". There is no factual basis, to derive "S" as the missing residue as opposed to "Q" or alternatively "S" or "Q" plus another amino acid at position 0 according to Kabat et al (Exhibit G of record). Declarant's position that it is actually "S" and was mutated from the closest germline sequence is speculative.

To summarize, the alledged errors are not obvious because the corresponding actual germline sequence from which the scFv sequence were derived is not known or reported in the specification and the using the closest match to determine actual positions and residues is speculative and flawed for reasons set forth above. The corrections are

not immediately obvious because the specific corresponding germlines are not known or disclosed and Kabat et al of record indicate that residues may occur at position 0. As such, the absence or presence of an additional residue cannot be ruled out and in view of the lack of showing how the cloning strategy, (which was not disclosed in the specification) necessarily led to insertion of "A", "AF" and "AL" residues. As such, the skilled artisan cannot recognize the correction of Applicants/Declarant as opposed to several possible corrections. There must be an obvious error and an obvious correction. The error is not obvious because the germline is not disclosed and the correction is not obvious because of the potential for an additional amino acid in view of Kabat et al (Exhibit G of record) and that Declarant did not describe how the cloning strategy, that is not specifically described in the specification, directly led to the insertion of the additional residues that were origionally disclosed as being part of the V_L domain. The error of a missing serine and use of the linker serine is also not obvious to the skilled artisan because the germline is not disclosed and the correction is not obvious because of (1) the potential for an additional amino acid in view of Kabat et al (Exhibit G of record); and (2) that Declarant did not describe how the cloning strategy directly led to the use of the terminal serine in the linker $(Gly_4Ser)_3$ in place of the germline serine, a serine residue that was NOT origionally disclosed as being part of the V_L domain. Further, in at least Footnote 4, the closest match is allegedly "Q" and Declarant provides no rationale that serine would necessarily be immediately recognized as the correction as presented in the amendments, as opposed to "Q" being missing which is the actual corresponding residue. Declarant speculates that the sequence has been mutated but cannot rule out the possibility that it was not and the cloning strategy "lost" the missing V_L residue or residues.

For the foregoing reasons, the Declartion of Rodger Smith and Applicants response does not provide a basis for correcting either the specification or claims as they relate to the metes and bounds of the V_L domains of the scFvs.

Claims 97-100, 119-127, 130-143, 146-152 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended to recite different delineations of the V_L domain. These different delineations correspond to corrections appearing in the amended specification filed 12-14-04. The errors in assignment of the V_L domain were asserted as obvious errors and were accompanied by a Declaration by Rodger Smith persuant to 37 CFR 1.132. The Declaration has been carefully considered but is not persuasive for reasons set forth above. Niether the errors or the corrections are obvious to the skilled artisan for reasons made of record supra.

As such, these claims that recite amended V_L domains are new matter.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645